

FORM PTO-1390 (MODIFIED) (REV 1-98)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			237.US	
			U.S. APPLICATION NO. (If an int. app. see 37 C.F.R. 1.53) <b>09/555442</b>	
INTERNATIONAL APPLICATION NO. <b>PCT/US98/26327</b>		INTERNATIONAL FILING DATE <b>10 December 1998 (10.12.98)</b>		PRIORITY DATE CLAIMED <b>12 December 1997 (12.12.97)</b>
TITLE OF INVENTION <b>CYCLOHEXENE CARBOXYLATES AS NEURAMINIDASE INHIBITORS</b>				
APPLICANT(S) FOR DO/EO/US <b>KIM, Choung U.; LEW, Willard</b>				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</p> <p>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p style="margin-left: 40px;">a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</p> <p style="margin-left: 40px;">b. <input type="checkbox"/> has been transmitted by the International Bureau.</p> <p style="margin-left: 40px;">c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</p> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p style="margin-left: 40px;">a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</p> <p style="margin-left: 40px;">b. <input type="checkbox"/> have been transmitted by the International Bureau.</p> <p style="margin-left: 40px;">c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p style="margin-left: 40px;">d. <input type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> <p>Items 11. to 16. below concern document(s) or information included:</p> <p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A FIRST preliminary amendment.</p> <p style="margin-left: 40px;"><input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input type="checkbox"/> Other items or information:</p>				

422 Rec'd PCT/PTO 31 MAY 2000

U.S. APPLICATION NO. (If known, file 37 CFR 1.53)		INTERNATIONAL APPLICATION NO.		ATTORNEY'S DOCKET NUMBER	
09/555442		PCT/US98/26327		237.US	
17. <input checked="" type="checkbox"/> The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO . . . . .				\$970.00	
International preliminary exam fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO . . . .				\$840.00	
International preliminary exam fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . .				\$690.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) . . . . .				\$670.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) . . . . .				\$96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 840.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	42 - 20 =	22	X \$18.00	\$ 396.00	
Independent Claims	7 - 3 =	4	X \$78.00	\$ 312.00	
Multiple dependent claims (if applicable)			+ \$270.00	\$	
TOTAL OF ABOVE CALCULATIONS				=	\$ 708.00
Reduction by 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL				=	\$
Processing fee of \$130.00 for furnishing English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE				=	\$ 1,548.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED				=	\$ 1,548.00
				Amount to be: refunded	\$
				charged	\$
a. <input type="checkbox"/> a check in the amount of _____ to cover the above fees is enclosed.					
b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 07-1250 in the amount of \$ 1,548.00 to cover the above fees. A duplicate copy of this sheet is enclosed.					
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 07-1250. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO:					
Max D. Hensley Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 Telephone: (650) 522-5878 Facsimile: (650) 522-5575					
SIGNATURE					
Max D. Hensley NAME					
27,043 REGISTRATION NUMBER					

5

CYCLOHEXENE CARBOXYLATES AS NEURAMINIDASE INHIBITORSBackground of the InventionField of the Invention

10 Neuraminidase (also known as sialidase, acylneuraminyl hydrolase, and EC 3.2.1.18) is an enzyme common among animals and a number of microorganisms. It is a glycohydrolase that cleaves terminal alpha-ketosidically linked sialic acids from glycoproteins, glycolipids and oligosaccharides. Many of the microorganisms containing neuraminidase  
15 are pathogenic to man and other animals including fowl, horses, swine and seals. These pathogenic organisms include influenza virus.

Neuraminidase has been implicated in the pathogenicity of influenza viruses. It is thought to help the elution of newly synthesized virions from infected cells and assist in the movement of the virus (through its hydrolase  
20 activity) through the mucus of the respiratory tract.

Brief Description of Related Art

von Itzstein, M. et al.; "Nature", 363(6428):418-423 (1993), discloses the rational design of sialidase-based inhibitors of influenza virus replication.

25 Colman, P. M. et al.; International Patent Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date April 30, 1992), Itzstein, L. M. von et al.; European Patent Publication No. 0 539 204 A1 (EP App. No. 92309684.6, publication date April 28, 1993), and von Itzstein, M. et al.; International Publication No. WO 91/16320 (Int. App. No.  
30 PCT/AU91/00161, publication date October 31, 1991) disclose compounds that bind neuraminidase and are asserted to exhibit antiviral activity *in vivo*.

Bischofberger, N. et al.; International Patent Publication No. WO 96/26933 (publication date September 6, 1996) and copending U.S.S.N.  
35 08/606,624 describe novel selective inhibitors of viral or bacterial neuraminidases.

### Objects of the Invention

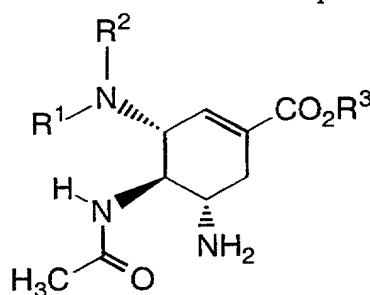
A principal object of the invention is inhibition of viruses, in particular influenza viruses. In particular, an object is inhibition of glycolytic enzymes such as neuraminidase, in particular the selective inhibition of viral or bacterial neuraminidases.

An additional object of the invention is to provide neuraminidase inhibitors that have a retarded rate of urinary excretion, that enter into nasal or pulmonary secretions from the systemic circulation, that have sufficient oral bioavailability to be therapeutically effective, that possess elevated potency, that exhibit clinically acceptable toxicity profiles and have other desirable pharmacologic properties.

These and other objects will be readily apparent to the ordinary artisan from consideration of the invention as a whole.

### Summary of the Invention

The present invention is directed to compounds of the formula (I):



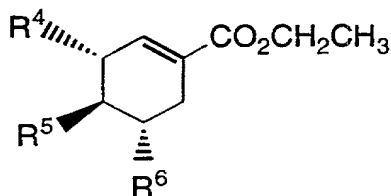
I

wherein:

- 20 R<sup>1</sup> is H, R<sup>2</sup> is -CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and R<sup>3</sup> is H;
- R<sup>1</sup> is H, R<sup>2</sup> is -CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>;
- R<sup>1</sup> is H, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is H;
- R<sup>1</sup> is H, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>;
- R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is H;
- 25 R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>;
- R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is H;
- R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>;
- R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and R<sup>3</sup> is H;
- R<sup>1</sup> is -CH<sub>3</sub>, R<sup>2</sup> is -CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>;

- $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
5  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $\text{H}$ ;  
10  $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2(\text{cyclopropyl})$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2(\text{cyclopropyl})$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
15  $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  $\text{H}$ ;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
 $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
 $\text{H}$ ;  
20  $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
 $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$  and  $R^3$  is  $\text{H}$ ;  
or  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$  and  $R^3$  is  
25  $-\text{CH}_2\text{CH}_3$ ;  
and salts, solvates and resolved enantiomers thereof.

The present invention is also directed to compounds of the formula  
 (II):



II

wherein:

$R^4$  is -OH,  $R^5$  is -NH<sub>2</sub> and  $R^6$  is -N<sub>3</sub>;

$R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N<sub>3</sub>;

$R^4$  is -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 5 -N(CH<sub>3</sub>)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>Ph),  
 -N(CH<sub>3</sub>)(cyclohexyl), -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>(cyclopropyl)), -(1-C<sub>4</sub>H<sub>8</sub>N), -(1-C<sub>5</sub>H<sub>10</sub>N), or -(1-C<sub>4</sub>H<sub>8</sub>NO);

$R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N<sub>3</sub>;

10  $R^4$  is -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 -N(CH<sub>3</sub>)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>Ph),  
 -N(CH<sub>3</sub>)(cyclohexyl), -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>(cyclopropyl)), -(1-C<sub>4</sub>H<sub>8</sub>N), -(1-C<sub>5</sub>H<sub>10</sub>N), or -(1-C<sub>4</sub>H<sub>8</sub>NO);

15  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>;

$R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>;

$R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is  
 -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);

$R^4$  is -N<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);

20  $R^4$  is -NH<sub>2</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);

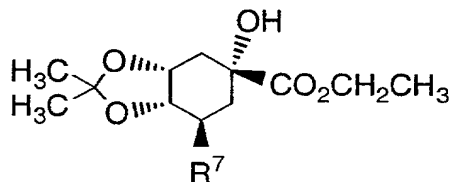
$R^4$  is -N(H)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or -N(H)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>),  $R^5$  is  
 -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);

$R^4$  is -N(H)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or -N(H)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>),  $R^5$  is  
 -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>; or

25  $R^4$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R^5$  is -NH<sub>2</sub> and  $R^6$  is -N<sub>3</sub>;

and salts, solvates and resolved enantiomers thereof.

The present invention is also directed to compounds of the formula  
 (III):



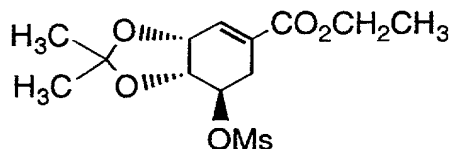
III

30

wherein:

$R^7$  is -OH or -OMs;  
and salts, solvates and resolved enantiomers thereof.

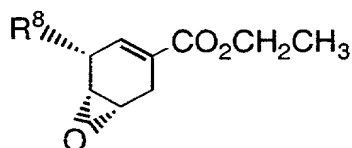
The present invention is also directed to compounds of the formula  
5 (IV):



IV

and salts, solvates and resolved enantiomers thereof.

The present invention is also directed to compounds of the formula  
10 (V):

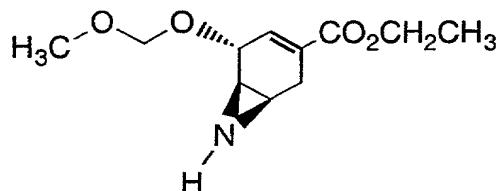


V

wherein:

$R^8$  is -OH, or -OCH<sub>2</sub>OCH<sub>3</sub>;  
15 and salts, solvates and resolved enantiomers thereof.

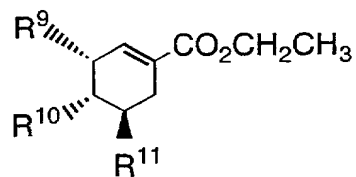
The present invention is also directed to compounds of the formula  
(VI):



VI

20 and salts, solvates and resolved enantiomers thereof.

The present invention is also directed to compounds of the formula (VII):



5

VII

;

wherein:

$R^9$  is -OH,  $R_{10}$  is -OH, and  $R_{11}$  is -OMs;

$R^9$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R_{10}$  is -OH, and  $R_{11}$  is -N<sub>3</sub>; or

$R^9$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R_{10}$  is -OMs, and  $R_{11}$  is -N<sub>3</sub>;

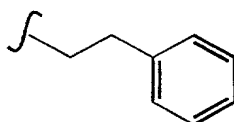
10 and salts, solvates and resolved enantiomers thereof.



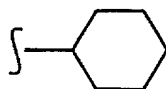
Detailed DescriptionCompositions of the Invention

The compositions of the invention are described above in the Summary of the Invention.

- 5 "Ph" means phenyl ( $-C_6H_5$ ), so that, for example, " $-CH_2CH_2Ph$ " means a group of the form:

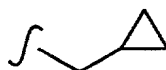


"Cyclohexyl" means a cyclohexane ring substituent ( $-C_6H_{11}$ ), so that, for example, " $-(cyclohexyl)$ " means a group of the form:



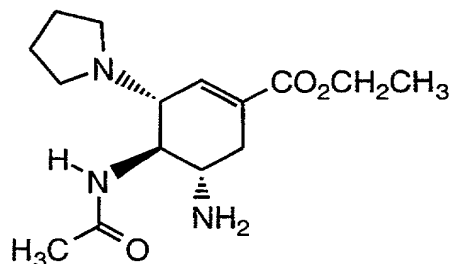
10

"Cyclopropyl" means a cyclopropane ring substituent ( $-C_3H_5$ ), so that, for example, " $-CH_2(cyclopropyl)$ " means a group of the form:



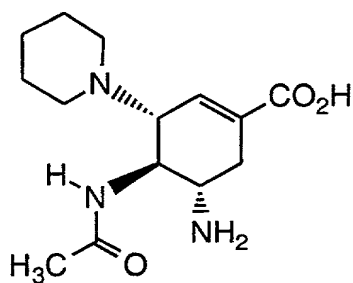
15

" $R^1$  and  $R^2$  are taken together to form  $-CH_2CH_2CH_2CH_2-$ " means that  $R^1$  and  $R^2$  are combined to form a divalent substituent bonded to the nitrogen atom, so that, for example, a compound of Formula (I) wherein  $R^1$  and  $R^2$  are taken together to form  $-CH_2CH_2CH_2CH_2-$  and  $R^3$  is  $-CH_2CH_3$ ; means a compound having the formula:



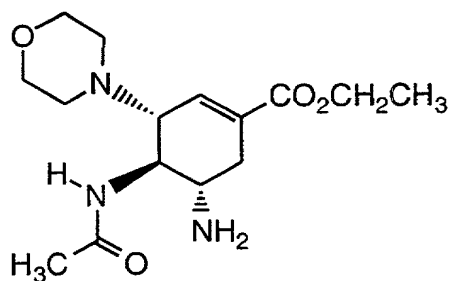
20

Similarly, a compound of formula (I) wherein  $R^1$  and  $R^2$  are taken together to form  $-CH_2CH_2CH_2CH_2CH_2-$  and  $R^3$  is H; means a compound having the formula:



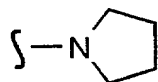
; and

a compound of formula (I) wherein  $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ; means a compound having the formula:



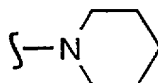
5

A substituent  $-(1-\text{C}_4\text{H}_8\text{N})$  is a group of the formula:

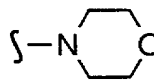


10

A substituent  $-(1-\text{C}_5\text{H}_{10}\text{N})$  is a group of the formula:

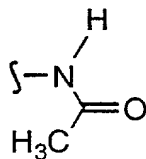


A substituent  $-(1-\text{C}_4\text{H}_8\text{NO})$  is a group of the formula:

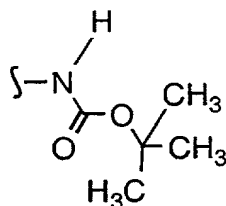


15

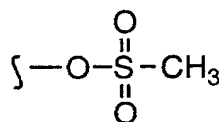
A substituent  $-\text{N}(\text{H})(\text{C}(\text{O})\text{CH}_3)$  is a group of the formula:



A substituent  $-\text{N}(\text{H})(\text{C}(\text{O})\text{OC}(\text{CH}_3)_3)$  is a group of the formula:



A substituent "-OMs" is a group of the formula:



5

### Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example,  $\text{Na}^+$ ,  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ . Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with the carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g.,  $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$ , or organic sulfonic acids, to basic centers, typically the amine. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or

leucine.

#### Methods of Inhibition of Neuraminidase

Another aspect of the invention relates to methods of inhibiting the  
5 activity of neuraminidase comprising the step of treating a sample suspected  
of containing neuraminidase with a compound of the invention.

Compositions of the invention act as inhibitors of neuraminidase or  
as intermediates for such inhibitors. The inhibitors will bind to locations on  
the surface or in a cavity of neuraminidase having a geometry unique to  
10 neuraminidase. Compositions binding neuraminidase may bind with  
varying degrees of reversibility. Those compounds binding substantially  
irreversibly are ideal candidates for use in this method of the invention. In  
a typical embodiment the compositions bind neuraminidase with a binding  
coefficient of less than  $10^{-4}\text{M}$ , more typically less than  $10^{-6}\text{M}$ , still more  
15 typically  $10^{-8}\text{M}$ .

Within the context of the invention samples suspected of containing  
neuraminidase include natural or man-made materials such as living  
organisms; tissue or cell cultures; biological samples such as biological  
material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum,  
20 saliva, tissue samples, and the like); laboratory samples; food, water, or air  
samples; bioproduct samples such as extracts of cells, particularly  
recombinant cells synthesizing a desired glycoprotein; and the like.  
Typically the sample will be suspected of containing an organism which  
produces neuraminidase, frequently a pathogenic organism such as a virus.  
25 Samples can be contained in any medium including water and organic  
solvent/water mixtures. Samples include living organisms such as  
humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition  
of the invention to the sample or it comprises adding a precursor of the  
30 composition to the sample. The addition step comprises any method of  
administration as described above.

If desired, the activity of neuraminidase after application of the  
composition can be observed by any method including direct and indirect  
methods of detecting neuraminidase activity. Quantitative, qualitative, and  
35 semiquantitative methods of determining neuraminidase activity are all  
contemplated. Typically one of the screening methods described above is

15

## 20

25

30

35

### Pharmaceutical Formulations and Routes of Administration

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like.

5 Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates  
10 such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the  
15 condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the  
20 compounds of this invention is that they are orally bioavailable and can be dosed orally; it is not necessary to administer them by intrapulmonary or intranasal routes. Surprisingly, (in view of, inter alia, Bamford, M. J., "J. Enzyme Inhibition" 10:1-6 (1995), and especially p. 15, first full paragraph), the anti-influenza compounds of WO 91/16320, WO 92/06691 and U.S.  
25 Patent 5,360,817 are successfully administered by the oral or intraperitoneal routes. See Example 161 infra.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention  
30 comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

35 The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in

unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active

5 ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

10 Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The  
15 active ingredient may also be presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder,  
20 lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.  
25 In one embodiment acid hydrolysis of the medicament is obviated by use of an enteric coating.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to  
30 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be  
35 formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for

example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which  
5 enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may  
10 comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also  
15 preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween<sup>®</sup> 60, Span<sup>®</sup> 80, cetostearyl  
20 alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to  
25 avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last  
30 three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Formulations suitable for topical administration to the eye also  
35 include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient.



The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth  
5 include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

10 Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration  
15 have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry  
20 powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of influenza A or B infections as described below.

Formulations suitable for vaginal administration may be presented as  
25 pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous  
30 and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose  
35 containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile

liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit  
5 daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of  
10 formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

15 Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

20 Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the compound is controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of  
25 the compound.

The effective dose of compound depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active influenza infection, the method of delivery, and the pharmaceutical formulation, and will be  
30 determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day, usually from about .01 to about 5 mg/kg body weight per day, and more typically, from about .05 to about 0.5 mg/kg body weight per day. For  
35 example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg

and 500 mg, and may take the form of single or multiple doses.

Therapeutic compounds of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections of the respiratory system, in particular influenza infection, the compositions of the invention are combined with antivirals (such as amantidine, rimantadine and ribavirin), mucolytics, expectorants, bronchodilators, antibiotics, antipyretics, or analgesics. Ordinarily, antibiotics, antipyretics, and analgesics are administered together with or in the same course of therapy with the compounds of this invention.

#### Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C<sup>14</sup> or H<sup>3</sup>) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no neuraminidase inhibitory activity of their

own.

Exemplary Methods of Making the Compounds of the Invention

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

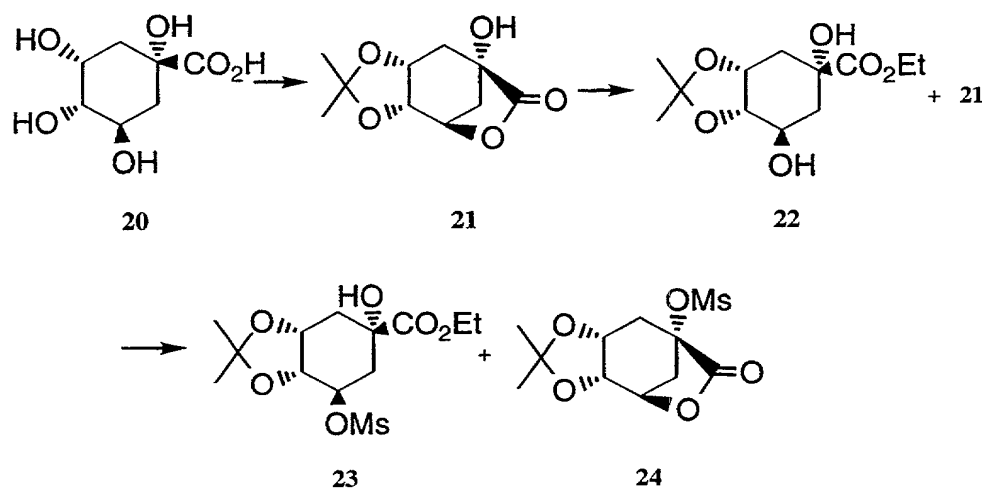
Condensation reactions are typically carried out at temperatures near

room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

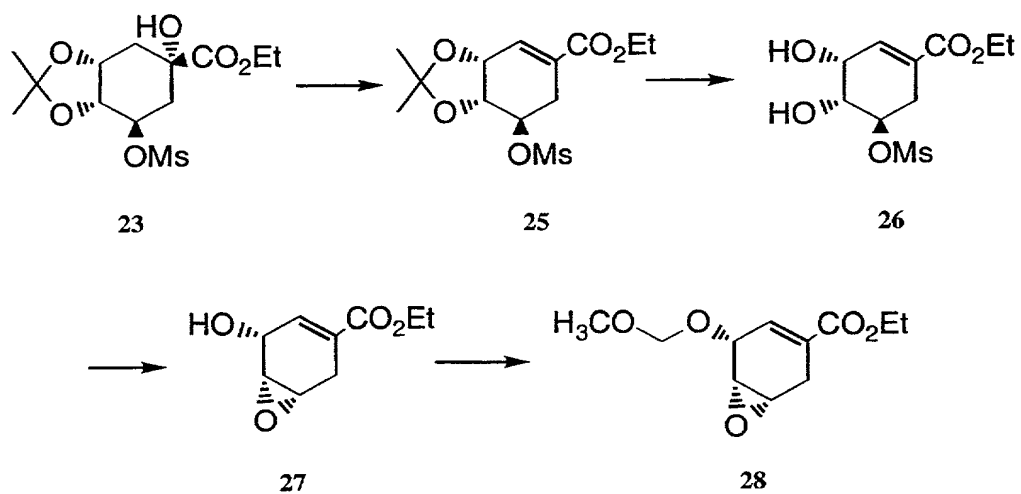
- 5           Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

          Exemplary methods of preparing compounds of the invention are shown in **Schemes 1-5** below. A detailed description of the methods are  
10       found in the Experimental section below.

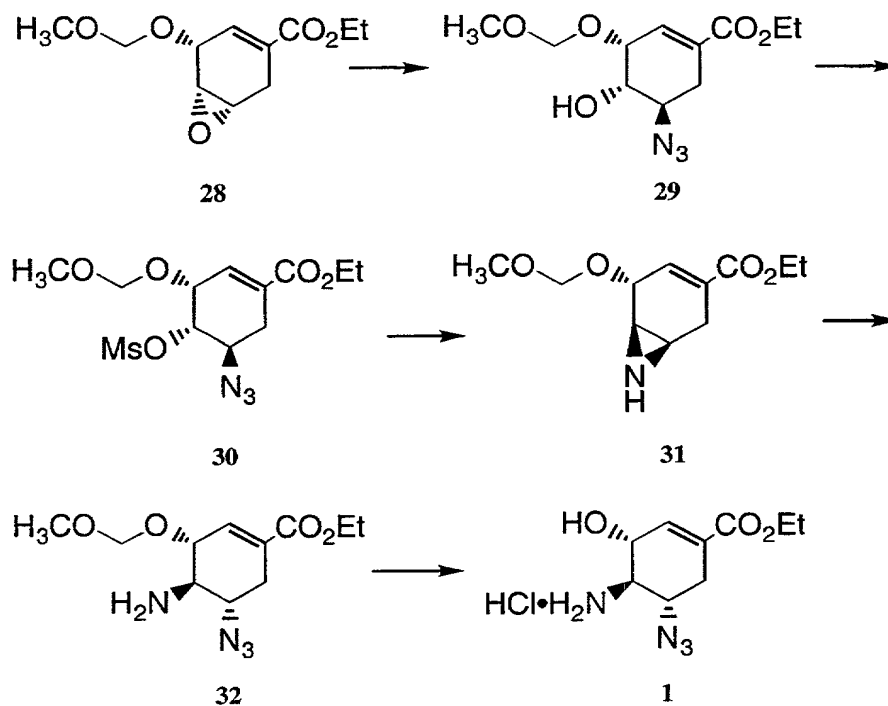
## Scheme 1



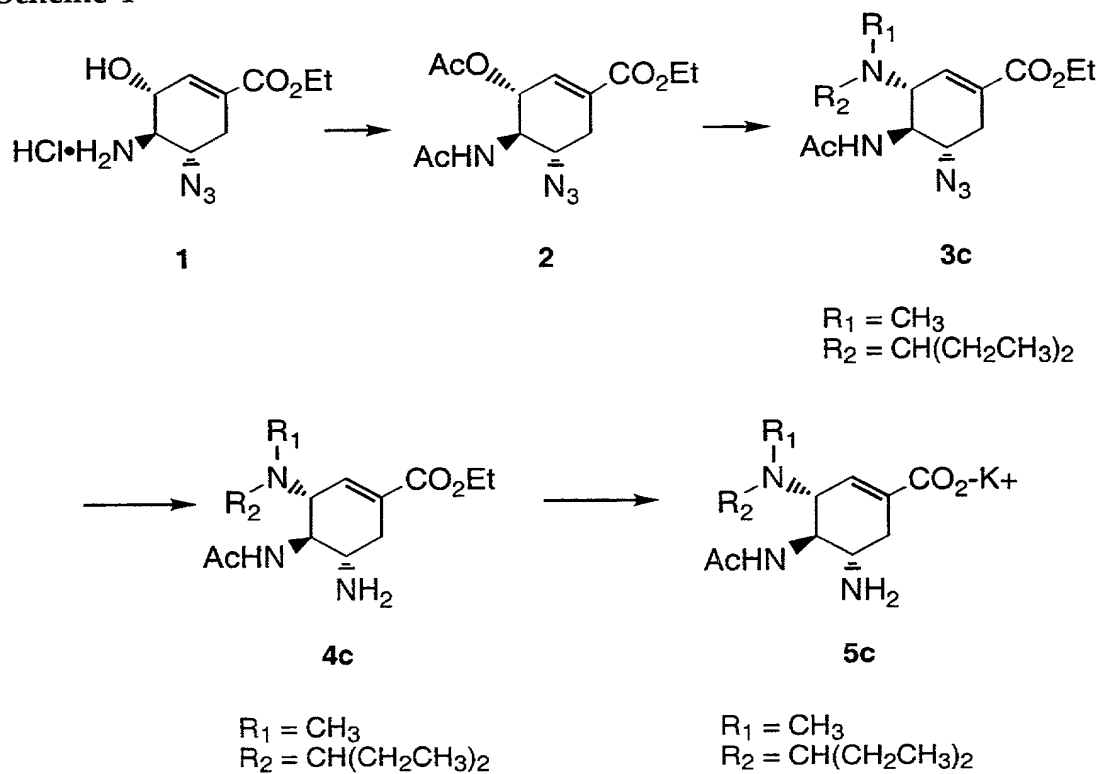
## 5 Scheme 2



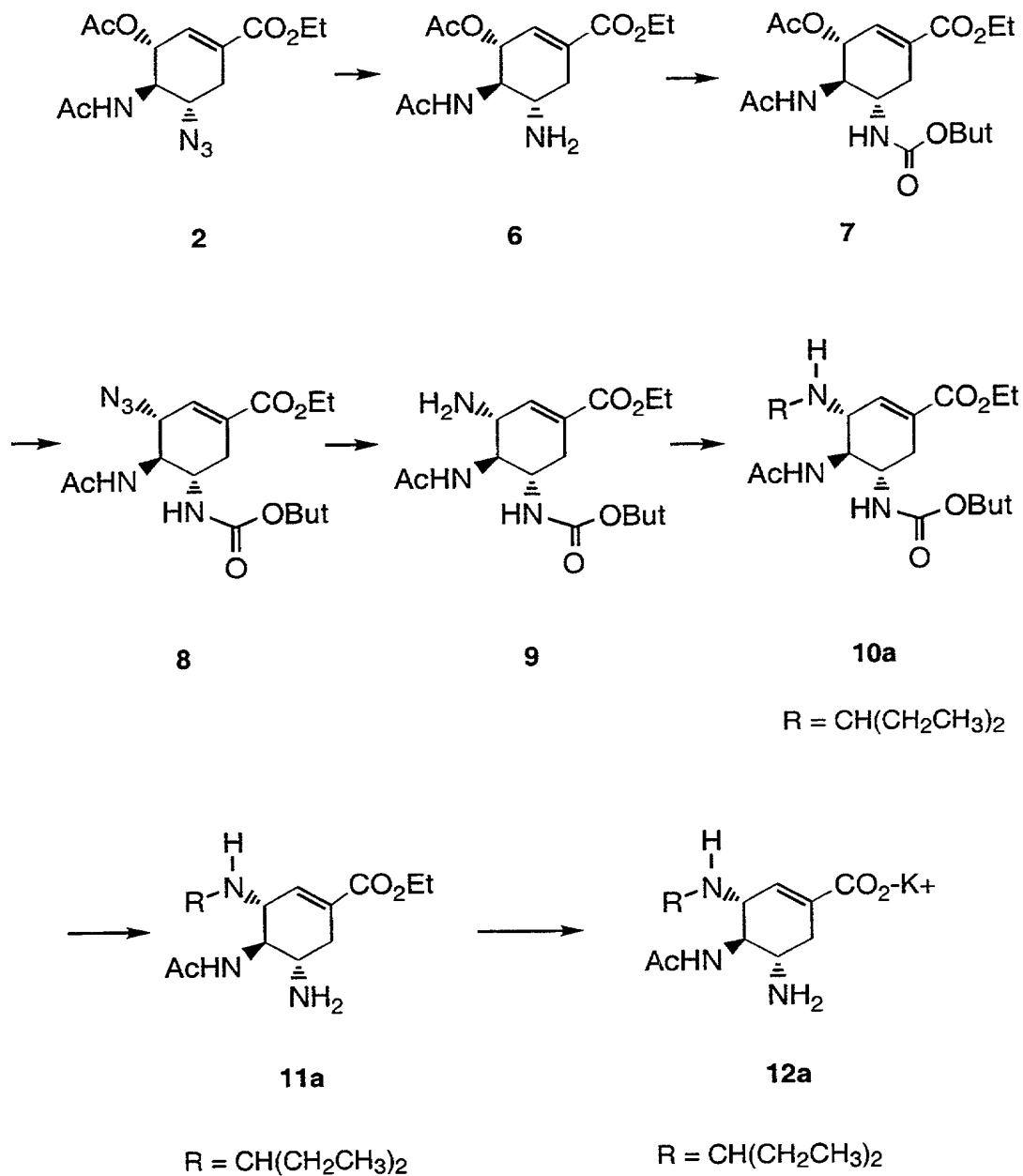
Scheme 3



Scheme 4



Scheme 5





General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

5       The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with  
10   compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with  
15   compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C),  
20   reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for  
25   "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

In each of the above exemplary schemes it may be advantageous to  
30   separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture,  
35   distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion

exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

- 5 Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the
- 10 reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

- 15 Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

- 20 All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the
- 25 following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.

## Examples

### General

The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated

- 5 Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted.
- 10 When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated. For example, the "corresponding acetate ester of compound 1" is Compound 2.

15

### Example 1

- Compound 21:** To a solution of **20** (Quinic Acid, 300 g, 1.56 mole) in acetone (1.1 L ) was added 2,2-dimethoxypropane ( 600 mL, 4.88 mole ) and p-toluenesulfonic acid monohydrate (3.0 g, 15.8 mmol). The mixture was
- 20 placed on a rotary evaporator at 60-65°C at atmospheric pressure for 3h. Solvents were evaporated and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, dried (MgSO<sub>4</sub>), filtered and evaporated to give **21** (260 g, 78 %) as a white solid.

25

### Example 2

- Compound 22:** To a solution of **21** (259 g, 1.21 mole) in absolute ethanol (1.34 L ) was added 20% sodium ethoxide in ethanol (5.9 mL, 16 mmol). The solution was stirred at ambient temperature for 2 h. Acetic acid
- 30 (1 mL, 18 mmol) was added and the solvents were distilled *in vacuo*. Ethyl acetate (600 mL) was added and the reaction was concentrated to near dryness. The solid residue was recrystallized from ethyl acetate/hexane to give an approximately 4.4:1 mixture of **22:21** ( 264 g, 84%) as a white crystalline solid which was used as is for the next reaction.

35

Example 3

**Compound 23:** To a solution of a mixture of **22** and **21** from the previous reaction (263 g, 1.01 mole) in dichloromethane (815 mL) cooled to -10 to 0°C was added methanesulfonyl chloride (78 mL, 1.01 mole) and triethylamine (195 mL, 1.4 mole). An additional portion of methanesulfonyl chloride (8 mL, 0.10 mole) in dichloromethane (200 mL) was added. After 2 h at -10 to 0°C, another portion of methanesulfonyl chloride (5 mL, 0.06 mole) was added. After an additional 1 h at -10 to 0°C, water (140 mL) and 3% hydrochloric acid (154 mL) were added. The organic layer was washed with water and evaporated. The residue was dissolved in ethyl acetate and cooled to -10° to -20°C for 2 h. After which compound **24** crystallized and was separated by filtration and washed with cold ethyl acetate. The filtrate was concentrated to give **23** (304 g, 89%) as an orange resin.

Example 4

**Compound 25:** To a solution of **23** (303 g, 0.895 mole) in pyridine (300 mL) and dichloromethane (1100 mL) cooled to -30 to -40°C was added sulfuric chloride (109 mL, 1.36 mole) dropwise. The mixture was stirred at -20 to -30°C for 1 h followed by the dropwise addition of methanol (53 mL) at -30 to -40°C. The reaction mixture was allowed to warm to room temperature and stirred at ambient temperature overnight. Acetic acid (8 mL) was added followed by the addition of hexane (800 mL) and then filtered. The filtrate was evaporated and diluted with ethyl acetate. The organic layer was washed with water, dried (MgSO<sub>4</sub>), filtered through a pad of silica gel and concentrated. The residue was precipitated from ethyl acetate and hexane to give **25** (189 g, 66%) as a red solid which contained ca. 20% of the corresponding olefin regioisomer.

Example 5

**Compound 26:** A mixture of **25** from the previous reaction (188 g, 0.587 mole) in ethanol (362 mL) was heated at 90 - 95°C with the continuous removal of solvent via distillation over a 3.5 h period. The reaction mixture was concentrated to give a solid residue which was recrystallized from ethyl acetate and hexane to give **26** (99 g, 60%) as a white solid.

Example 6

**Compound 27:** To a solution of **26** (96.5 g, 0.344 mole) in anhydrous THF (750 mL) at 0°C was added 1,8-Diazabicyclo [5.4.0] undec-7-ene (54 mL, 0.361 mole) dropwise. The mixture was stirred at 0°C for 2 h and then at ambient temperature overnight. Acetic acid (1.2g) was added and the reaction mixture was concentrated. The residue was dissolved in ethyl acetate/hexane (1/1) and filtered through a pad of silica gel. The filtrate was concentrated and precipitated from ethyl acetate and hexane to give **27** (58 g, 91%) as a white solid.

Example 7

**Compound 28:** To a solution of **27** (56.6 g, 0.307 mole) in dichloromethane (654 mL) were added N,N-Diisopropylethylamine (161 mL, 0.923 mole) and chloromethyl methyl ether (46.7 mL, 0.615 mole). The mixture was refluxed for 3 h, evaporated and partitioned between ethyl acetate and water. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered and evaporated to give **28** (70.2 g, 100 %) as a yellow oil.

Example 8

**Compound 29:** To a solution of **28** (70.2 g, 0.307 mole) in ethanol (1.09 L) and water (218 mL) was added sodium azide (100 g, 1.54 mole) and ammonium chloride (36.2 g, 0.677 mole). The mixture was gently refluxed for 2 h followed by the addition of water (200 mL). Volatiles were removed under reduced pressure followed by extraction of the aqueous layer with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give **29** (82 g, 98%) as a yellow oil.

Example 9

**Compound 30:** To a solution of **29** (81.7 g, 0.301 mole) in dichloromethane (690 mL) cooled to 0°C was added triethylamine (58.8 mL, 0.422 mole) and methanesulfonyl chloride ( 28 mL, 0.362 mole). The solution was stirred at 0°C for 2 h and then at ambient temperature for 30 min. Solvents were evaporated and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate, combined, washed with water, dried (MgSO<sub>4</sub>), filtered and

evaporated to give crude **30** (109 g) as a yellow oil.

#### Example 10

**Compound 31:** To a solution of crude **30** (109 g, 0.301 mole) in anhydrous THF (570 mL) cooled to 15 - 20°C was added triphenylphosphine (86.9 g, 0.331 mole) in anhydrous THF (120 mL) dropwise. The mixture was stirred at ambient temperature for 4.5 h followed by the addition of triethylamine (50.4 mL, 0.362 mole) and water (12 mL). The solution was stirred at ambient temperature overnight, evaporated and partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate, combined, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. Triphenylphosphine oxide which was precipitated from the crude product with ether and hexane was separated by filtration. The filtrate was concentrated and the residue was purified by filtration through a short column of silica gel eluting with ethyl acetate/methanol to give **31** (55.2 g, 81%) as a yellow oil.

#### Example 11

**Compound 32:** To a solution of **31** (55 g, 0.242 mole) in N,N-dimethylformamide (560 mL) was added sodium azide (78.7 g, 1.21 mole) and ammonium chloride (25.9 g, 0.484 mole). The mixture was stirred at 65°C for 18 h, cooled, diluted with dichloromethane (500 mL) and filtered. The filtrate was concentrated and filtered through a pad of silica gel eluting with ethyl acetate/hexane (1:1) to give **32** (59.2 g, 91%) as a yellow oil.

#### Example 12

**Compound 1:** A mixture of **32** (59.2 g, 0.22 mole) and HCl/ethanol (6.2% w/w, 520 mL) was stirred at ambient temperature for 8 h. Solvents were evaporated and the residue was precipitated from ether to give **1** (50.2 g, 87 %) as a brown solid.

#### Example 13

**Compound 2:** To a solution of alcohol **1** (2.0 g, 7.61 mmol) in dry pyridine (25 mL) at ambient temperature was added catalytic 4-dimethylamino pyridine (ca. 50 mg) and acetic anhydride (3.0 mL, 31.8 mmol). The reaction mixture was stirred for 24 h at ambient temperature,

concentrated and partitioned between ethyl acetate and water. The organic layer was separated and sequentially washed with 1 N HCl, water, satd. NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Concentration *in vacuo* gave a solid which was recrystallized from ethyl acetate/hexane to give 1.9 g (81%) of 2 as an off-white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.65 (t, J = 2.1 Hz, 1H); 5.70-5.66 (m, 2H); 4.23 (q, J = 7.2 Hz, 2H); 4.15-4.04 (m, 1H); 3.82-3.74 (m, 1H); 3.00-2.91 (m, 1H); 2.46-2.34 (m, 1H); 2.11 (s, 3H); 2.03 (s, 3H); 1.31 (t, J = 7.2 Hz, 3H).

#### Example 14

**Compound 3c:** To a solution of 2 (360 mg, 1.16 mmol) in dry THF (4.8 mL) was added Tetrakis(triphenylphosphine)palladium(0) (67.0 mg, 0.058 mmol) and N-methyl(1-ethyl propyl)amine (294 mg, 2.90 mmol). The mixture was refluxed for 4 h, concentrated and purified by chromatography eluting with ethyl acetate/hexane (3:7) to give 3c (153 mg, 38%) as an orange oil.

#### Example 15

**Compound 4c:** To a solution of azide 3c (153 mg, 0.435 mmol) in THF (6.5 mL) was added triphenylphosphine (172 mg, 0.656 mmol) and water (783 μL). The solution was heated at 50°C for 10 h and concentrated. The residue was diluted with ethyl acetate, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. Purification of the residue by chromatography eluting with ethyl acetate/methanol (7:3) gave 4c (75 mg, 53%). HRMS (FAB) calcd for C<sub>17</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub> (MH<sup>+</sup>) 326.2443, found 326.2443.

#### Example 16

**Compound 5c:** To a solution of 4c (59 mg, 0.181 mmol) in THF (1.48 mL) was added 0.974 N potassium hydroxide (186 μL, 0.181 mmol). The reaction mixture was stirred at ambient temperature for 24 h. Solvents were evaporated and the residue was purified by C<sub>18</sub> chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to afford 5c (50 mg, 83 %) as an off-white solid. <sup>1</sup>H NMR (D<sub>2</sub>O) δ 6.55 (s, 1H), 3.73 (t, J=11 Hz, 1H), 3.55 (m, 1H), 2.82 (m, 1H), 2.62 (m, 1H), 2.36 (m, 1H), 2.19 (s, 3H), 2.06 (m, 1H), 2.03 (s, 3H), 1.36-1.48 (m, 4H), 0.86 (m, 6H); HRMS (FAB) calcd for C<sub>15</sub>H<sub>27</sub>KN<sub>3</sub>O<sub>3</sub> (MH<sup>+</sup>) 336.1689, found 336.1698.

#### Example 17

**Compounds 5a, 5b, 5d, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l, 5m:** Prepared from 2 by a method similar to that described for 5c.

#### Example 18

5       **Compound 6:** To a solution of 2 (1.02 g, 3.28 mmol) in THF (49 mL) was added triphenylphosphine (1.29 g, 4.9 mmol) and water (5.9 mL). The mixture was heated at 50°C for 10 h. Solvents were evaporated and the residue was diluted with ethyl acetate, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography eluting with ethyl  
10       acetate/methanol (4:1) to give 6. HRMS (FAB) calcd for C<sub>13</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub> (MH<sup>+</sup>) 285.1450, found 285.1452.

#### Example 19

15       **Compound 7:** To a solution of 6 (920 mg, 3.24 mmol) in dry acetonitrile (19 mL) was added Di-*tert*-butyl dicarbonate (884 mg, 4.05 mmol). The mixture was stirred at ambient temperature for 2.5 h and concentrated to give a residue which was precipitated from ethyl acetate and hexane to give 7 (1.25 g, 100%) as a colorless solid. HRMS (FAB) calcd for C<sub>18</sub>H<sub>29</sub>N<sub>2</sub>O<sub>7</sub> (MH<sup>+</sup>) 385.1974, found 385.1981.

#### Example 20

20       **Compound 8:** To a solution of 7 (1.0 g, 2.60 mmol) in THF (6.6 mL) and water (2.3 mL) was added Tetrakis(triphenylphosphine)palladium(0) (91 mg, 0.079 mmol) and sodium azide (190 mg, 2.92 mmol). The solution was  
25       heated at 75°C for 3 h and then extracted with ethyl ether. The combined organic extracts were washed with 2N HCl, saturated sodium bicarbonate, brine, dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography eluting with ethyl acetate/hexane (4:6) to give 8 (610 mg, 64%) as an off white solid. HRMS (FAB) calcd for C<sub>16</sub>H<sub>26</sub>N<sub>5</sub>O<sub>5</sub> (MH<sup>+</sup>)  
30       368.1934, found 368.1927.

#### Example 21

35       **Compound 9:** To a solution of azide 8 (650 mg, 1.77 mmol) in THF (26 mL) was added triphenylphosphine (697 mg, 2.66 mmol) and water (3.25 mL). The solution was heated at 50°C for 10 h. Solvents were evaporated and the residue diluted with ethyl acetate, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and



evaporated. The residue was purified by chromatography eluting with ethyl acetate/methanol (4:1) to give **9** (551 mg, 91%). HRMS (FAB) calcd for  $C_{16}H_{28}N_3O_5$  ( $MH^+$ ) 342.2029, found 342.2031.

5 Example 22

**Compound 10a:** To a solution of **9** (200 mg, 0.586 mmol) in anhydrous methanol (1.7 mL) was added 3-pentanone (119  $\mu$ L, 1.17 mmol) followed by the addition of a solution of  $NaCNBH_3$  (74 mg, 1.17 mmol) and  $ZnCl_2$  (80 mg, 0.587 mmol) in anhydrous methanol (1.7 mL). The mixture  
10 was stirred at ambient temperature for 26 h and quenched with saturated ammonium chloride. Volatiles were removed under reduced pressure followed by extraction with ethyl ether. The combined organic extracts were washed with saturated sodium bicarbonate, brine, dried ( $Na_2SO_4$ ), filtered through a thin pad of silica gel and evaporated to give **10a** (168 mg, 70%) as a  
15 colorless solid. HRMS (FAB) calcd for  $C_{21}H_{38}N_3O_5$  ( $MH^+$ ) 412.2811, found 412.2801.

Example 23

**Compound 11a:** Compound **10a** (161 mg, 0.391 mmol) was dissolved  
20 in trifluoroacetic acid (10% in  $CH_2Cl_2$ , 8.8 mL). The mixture was stirred at ambient temperature for 2.5 h and evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate, dried ( $Na_2SO_4$ ), filtered and evaporated. The residue was purified by chromatography eluting with ethyl acetate/methanol (6:4) to give **11a** (107 mg, 86%). HRMS  
25 (FAB) calcd for  $C_{16}H_{30}N_3O_3$  ( $MH^+$ ) 312.2287, found 312.2290.

Example 24

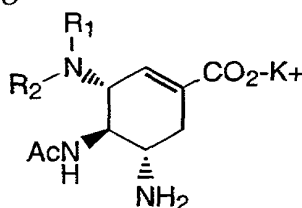
**Compound 12a:** To a solution of **11a** (50 mg, 0.161 mmol) in THF (1.32 mL) was added 0.974 N potassium hydroxide (165  $\mu$ L, 0.161 mmol). The  
30 reaction mixture was stirred at ambient temperature for 21 h. Solvents were evaporated and the residue was purified by  $C_{18}$  chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to afford **12a** (40 mg, 77 %) as an off-white solid.  $^1H$  NMR ( $D_2O$ )  $\delta$  6.40 (s, 1H), 3.56 (t,  $J = 11$  Hz, 1H), 3.38 (m, 1H), 2.87 (m, 1H), 2.64 (m, 1H),  
35 2.54 (m, 1H), 2.09 (m, 1H), 2.06 (s, 3H), 1.40 (m, 4H), 0.82 (m, 6H); HRMS (FAB) calcd for  $C_{14}H_{25}KN_3O_3$  ( $MH^+$ ) 322.1533, found 322.1532.

Example 25

**Compound 12b:** The title compound was prepared in 33% yield from amine 9 by a method similar to that described for compound 12a. <sup>1</sup>H NMR (D<sub>2</sub>O) δ 6.35 (s, 1H), 3.69 (t, *J* = 11 Hz, 1H), 3.38 (m, 1H), 2.84 (m, 1H), 2.64 (m, 1H), 2.42-2.55 (m, 2H), 2.08 (m, 1H), 2.04 (s, 3H), 1.42 (m, 2H), 0.85 (m, 3H); C<sub>12</sub>H<sub>20</sub>KN<sub>3</sub>O<sub>3</sub> (MH<sup>+</sup>) 294.1220, found 294.1221.

Example 26

**Enzyme Inhibition:** Using the methods of screening *in vitro* activity described above, the following activities were observed:



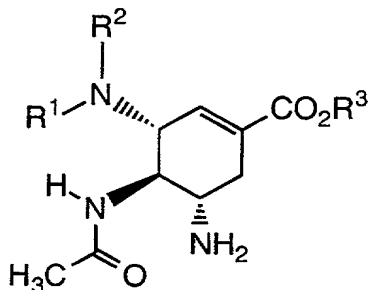
compound	R <sub>1</sub>	R <sub>2</sub>	Neuraminidase Flu A	IC <sub>50</sub> (nM) Flu B
12a	H	CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	11.5	100
12b	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	200	240
5a	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	65	65
5b	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	180	ND
5c	CH <sub>3</sub>	CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	6	60
5d	CH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	120	ND
5e	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	100	565
5f	CH <sub>3</sub>	C <sub>6</sub> H <sub>11</sub>	200	>1000
5g	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	90	ND
5h	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	85	175
5i	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	12	60
5j	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> C <sub>3</sub> H <sub>5</sub>	50	ND
5k	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -		400	ND
5l	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -		30	3
5m	-CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> -		200	30

ND means No Data.

- All literature and patent citations above are hereby expressly incorporated by reference in their entirety at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail
- 5 sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.

What is claimed is:

1. A compound of the formula (I):



5 wherein:

- $R^1$  is H,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is H;  
 $R^1$  is H,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is H,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 $R^1$  is H,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 10  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is H;  
 15  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 20  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 25  $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2(\text{cyclopropyl})$  and  $R^3$  is H;

- $R^1$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2(\text{cyclopropyl})$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is H;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
 $-\text{CH}_2\text{CH}_3$ ;  
5  $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
H;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $R^3$  is  
 $-\text{CH}_2\text{CH}_3$ ;  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$  and  $R^3$  is H;  
10 or  
 $R^1$  and  $R^2$  are taken together to form  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$  and  $R^3$  is  
 $-\text{CH}_2\text{CH}_3$ ;  
and salts, solvates and resolved enantiomers thereof.
- 15 2. The compound of Claim 1 wherein  $R^1$  is H,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$   
and  $R^3$  is H.
- 20 3. The compound of Claim 1 wherein  $R^1$  is H,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$   
and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
4. The compound of Claim 1 wherein  $R^1$  is H,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  
 $R^3$  is H.
- 25 5. The compound of Claim 1 wherein  $R^1$  is H,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  
 $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
6. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$   
and  $R^3$  is H.
- 30 7. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$   
and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
8. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H.
- 35

9. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
10. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is H.
11. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
12. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is H.
13. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
14. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is H.
15. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{Ph}$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
16. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is H.
17. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_3$ ,  $R^2$  is  $-(\text{cyclohexyl})$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
18. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H.
19. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is  $-\text{CH}_2\text{CH}_3$ .
20. The compound of Claim 1 wherein  $R^1$  is  $-\text{CH}_2\text{CH}_3$ ,  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$  and  $R^3$  is H.

21. The compound of Claim 1 wherein R<sup>1</sup> is -CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

22. The compound of Claim 1 wherein R<sup>1</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is H.

23. The compound of Claim 1 wherein R<sup>1</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

24. The compound of Claim 1 wherein R<sup>1</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>(cyclopropyl) and R<sup>3</sup> is H.

25. The compound of Claim 1 wherein R<sup>1</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R<sup>2</sup> is -CH<sub>2</sub>(cyclopropyl) and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

26. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is H.

27. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

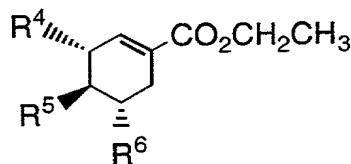
28. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is H.

29. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

30. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is H.

31. The compound of Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>- and R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>.

32. A compound of the formula (II):



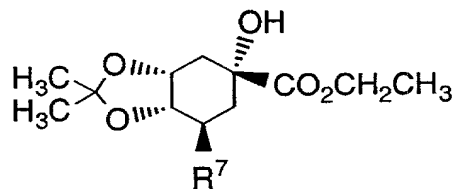
II

wherein:

- 5         $R^4$  is -OH,  $R^5$  is -NH<sub>2</sub> and  $R^6$  is -N<sub>3</sub>;  
           $R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N<sub>3</sub>;  
           $R^4$  is -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
          -N(CH<sub>3</sub>)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>Ph),  
          -N(CH<sub>3</sub>)(cyclohexyl), -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
 10       -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
          -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>(cyclopropyl)), -(1-C<sub>4</sub>H<sub>8</sub>N), -(1-C<sub>5</sub>H<sub>10</sub>N), or -(1-C<sub>4</sub>H<sub>8</sub>NO),  
           $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N<sub>3</sub>;  
           $R^4$  is -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
          -N(CH<sub>3</sub>)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>Ph),  
 15       -N(CH<sub>3</sub>)(cyclohexyl), -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
          -N(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>),  
          -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>(cyclopropyl)), -(1-C<sub>4</sub>H<sub>8</sub>N), -(1-C<sub>5</sub>H<sub>10</sub>N), or -(1-C<sub>4</sub>H<sub>8</sub>NO),  
           $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>;  
           $R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>;  
 20        $R^4$  is -OC(O)CH<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is  
          -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);  
           $R^4$  is -N<sub>3</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);  
           $R^4$  is -NH<sub>2</sub>,  $R^5$  is -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);  
           $R^4$  is -N(H)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or -N(H)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>),  $R^5$  is  
 25       -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -N(H)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>);  
           $R^4$  is -N(H)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or -N(H)(CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>),  $R^5$  is  
          -N(H)(C(O)CH<sub>3</sub>) and  $R^6$  is -NH<sub>2</sub>; or  
           $R^4$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R^5$  is -NH<sub>2</sub> and  $R^6$  is -N<sub>3</sub>;  
          and salts, solvates and resolved enantiomers thereof.



33. A compound of the formula (III):



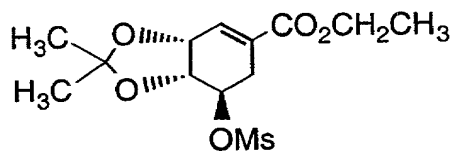
III

;

wherein:

- 5             $R^7$  is -OH or -OMs;  
and salts, solvates and resolved enantiomers thereof.

34. A compound of the formula (IV):

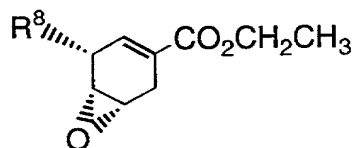


IV

10

and salts, solvates and resolved enantiomers thereof.

35. A compound of the formula (V):



V

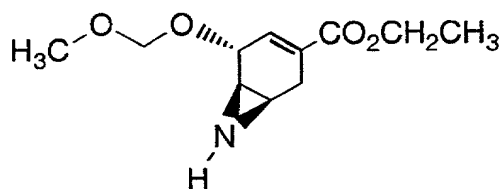
15

wherein:

- $R^8$  is -OH, or -OCH<sub>2</sub>OCH<sub>3</sub>;  
and salts, solvates and resolved enantiomers thereof.

20

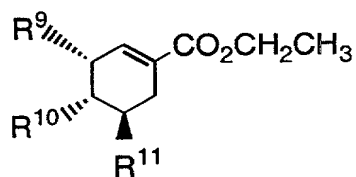
36. A compound of the formula (VI):



VI

and salts, solvates and resolved enantiomers thereof.

37. A compound of the formula (VII):



VII

5

wherein:

$R^9$  is -OH,  $R_{10}$  is -OH, and  $R_{11}$  is -OMs;

$R^9$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R_{10}$  is -OH, and  $R_{11}$  is -N<sub>3</sub>; or

$R^9$  is -OCH<sub>2</sub>OCH<sub>3</sub>,  $R_{10}$  is -OMs, and  $R_{11}$  is -N<sub>3</sub>;

10 and salts, solvates and resolved enantiomers thereof.

38. A compound of Claim 1 further comprising a pharmaceutically-acceptable carrier.

15 39. A method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with a compound of Claim 1.

20 40. The method of Claim 39 wherein the neuraminidase is influenza neuraminidase *in vivo*.

25 41. A method for the treatment or prophylaxis of influenza infection in a host comprising administering to the host a therapeutically effective amount of a compound of Claim 1.

42. The method of Claim 41 wherein the compound further comprises a pharmaceutically-acceptable carrier.

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)  
Approved for use through 9/30/00. OMB 0651-0032  
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

**DECLARATION FOR UTILITY OR  
DESIGN  
PATENT APPLICATION  
(37 CFR 1.63)**

☐ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number 237 . US

First Named Inventor KIM, Choung U.

**COMPLETE IF KNOWN**

Application Number /

Filing Date May 31, 2000

Group Art Unit

Examiner Name

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**CYCLOHEXENE CARBOXYLATES AS NEURAMINIDASE INHIBITORS**

the specification of which (Title of the Invention)

☐ is attached hereto  
OR

☒ was filed on (MM/DD/YYYY) 12/10/98 as United States Application Number or PCT International

Application Number US98/26327 and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.
60/069,553	12/12/97	

[Page 1 of 2]

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)  
Approved for use through 9/30/00. OMB 0651-0032  
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

## DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/US98/26327	12/10/98	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number

OR

☒ Registered practitioner(s) name/registration number listed below

Place Customer Number Bar Code Label here

Name	Registration Number	Name	Registration Number
Mark L. Bosse	35,071	Max D. Hensley	27,043

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.


Direct all correspondence to: ☐ Customer Number or Bar Code Label ☐ OR ☒ Correspondence address below

Name	Mark L. Bosse				
Address	GILEAD SCIENCES, INC.				
Address	333 Lakeside Drive				
City	Foster City	State	CA	ZIP	94404
Country	US	Telephone	(650) 522-5569	Fax	(650) 522-5575

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))		Family Name or Surname					
Choung U.		KIM					
Inventor's Signature			Date	5-30-00			
Residence: City	San Carlos	State	CA	Country	US	Citizenship	US
Post Office Address	1750 Elizabeth Street CA.						
Post Office Address							
City	San Carlos	State	CA	ZIP	94070	Country	US

☒ Additional inventors are being named on the supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → +

PTO/SB/02A (3-97)  
Approved for use through 9/30/98. OMB 0651-0032  
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

## DECLARATION

### ADDITIONAL INVENTOR(S)

#### Supplemental Sheet

Page 1 of 1

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])

Family Name or Surname

Willard

LEW

Inventor's  
Signature

Date

5/30/00

Residence: City

San Mateo

State

CA

Country

US

Citizenship

US

Post Office Address

717 Guildford Avenue

CA

Post Office Address

City

San Mateo

State

CA

ZIP

94402

Country

US

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])

Family Name or Surname

Inventor's  
Signature

Date

Residence: City

State

Country

Citizenship

Post Office Address

Post Office Address

City

State

ZIP

Country

Name of Additional Joint Inventor, if any:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])

Family Name or Surname

Inventor's  
Signature

Date

Residence: City

State

Country

Citizenship

Post Office Address

Post Office Address

City

State

ZIP

Country

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.